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EXAMINER	
GUCKER, STEPHEN	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/036,614
Filing Date: March 06, 1998
Appellant(s): HILLMAN ET AL.

Richard C. Ekstrom
and
Joel Harris
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/17/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) References of Record

5,194,596	Tischer et al.	03/1993
5,350,836	Kopchick et al.	09/1994

Benjamin et al., 1998, Development 125:1591-1598.

Vukicevic et al., 1996, PNAS USA 93:9021-9026.

Massague, 1987, Cell 49:437-438.

Pilbeam et al., 1993, Bone 14:717-720.

Skolnick et al., 2000, Trends in Biotech. 18:34-39.

Bork, 2000, Genome Research 10:398-400.

Doerks et al., 1998, Trends in Genetics 14:248-250.

Smith et al., 1997, Nature Biotechnology 15:1222-1223.

Brenner, 1999, Trends in Genetics 15:132-133.

Bork et al., 1996, Trends in Genetics 12:425-427.

Bowie et al., 1990, Science 247:1306-1310.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. § 101

Claims 22-29 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, or a well established utility. The instant claims are drawn to polynucleotides, vectors, host cells, and method of making an encoded polypeptide that are based on the genus of encoding sequences that encode the amino acid sequence of SEQ ID NO:1 or a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:1, of which SEQ ID NO:2 is a member of this genus (SEQ ID NO:2 is a specific polynucleotide sequence that encodes the amino acid sequence of SEQ ID NO:1). The asserted utilities for this genus of nucleic acids are that they provide beneficial uses in toxicology, drug development, and the diagnosis of disease (Brief, page 3). SEQ ID NO:1 is called a "Kinesin Light Chain Homolog" or a KILCH polypeptide by the specification. It was first identified as a clone from a human aortic smooth muscle cell line derived from explanted heart tissue obtained from a heart transplant (specification, page 44). A cDNA library was constructed and sequences were identified using a computer search for amino acid sequence alignments (specification, pages 46-47). KILCH is not disclosed to have been isolated or purified from any source or recombinantly produced from its encoding nucleic acids, so the protein has never been purified or made by scientists so no quantitative or functional assays have ever been performed on KILCH and no biological functions have been ascribed to KILCH as a result of any data generated from assays on the protein itself. The disclosure does teach that KILCH shares 66% sequence identity with human kinesin light chain polypeptide, along with other conserved structural features such as putative phosphorylation sites and heptad repeats (Brief, pages 2-3). Kinesin light chain (KLC)

and kinesin heavy chain (KHC) comprise an intracellular protein called kinesin that is known to be involved in the intracellular transport of membrane bound vesicles and organelles. Although the protein kinesin is involved in intracellular transport, the prior art of record relied on by the specification to assign functionality and utility for members of the kinesin family of proteins is drawn to the importance and functionality of the KHC and relatively little is known in comparison about the importance and functionality of the KLC (this contention by the Examiner is undisputed; see the instant specification on page 3, lines 11-18), and absolutely nothing is known about the pathological importance and/or functionality of the KILCH of the instant invention, other than the prophetic teachings of the disclosure. KILCH has not been demonstrated by any data or sound scientific reasoning to possess any of the biological functions ascribed to it by the specification for its asserted utilities as a diagnostic or a therapeutic. The disclosure teaches that KILCH and its encoding polynucleotides are useful in the diagnosis, treatment, and prevention of neurological, reproductive, and cell proliferative disorders. KILCH polynucleotide is expressed in various libraries, at least 47% of which are associated with cancer and cell proliferation. However, many polynucleotides are expressed constituently in both normal control *and* cancer and cell proliferation libraries as ubiquitous sequences found in all cells of a certain tissue type, healthy or not. The fact that KILCH is found in some libraries associated with cancer and cell proliferation or other tissues does not mean that it can be used as a useful marker for such without forcing further research to be performed (analysis of frequency of false positives and false negatives, validity, predictability, etc.). Likewise, the use of encoding polynucleotides for KILCH as a therapeutic for the multitude of diseases listed in the specification is not substantial because these diseases represent a multitude of different pathologies in their underlying or contributing causes, their varied symptomatology, and

differing avenues of treatment. Not a single one of the diseases recited as a boilerplate laundry-list has been shown to be associated in any way with the instant invention, either in the art of record or by a single scrap of scientific datum provided by Appellant. Other than being diseases of neurons or proliferation, the diseases listed do not have a single common unifying feature or mechanism underlying them that would lead the skilled artisan to believe that any single agent could treat all of them. This is particularly true when the agents of the instant invention have no specifically known demonstrated function in normal healthy cells, let alone in diseased cells, other than they partially comprise a protein involved in intracellular transport (kinesin).

These aforementioned utilities are not considered to be specific and substantial because the specification fails to disclose sufficiently any particular function or biological significance for KILCH or its encoding nucleotides of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to one other known protein, KLC, which little is known about itself and which has no demonstrated or art accepted connection to any known specific disease or disorder. For instance, there are no known diseases or treatments of record that rely on the presence or absence of KLC (a known protein of the prior art), or that rely on KLC's proper specific functioning, whatever that specific function may be, in order for a physician to diagnose or treat any known condition. After further research, a specific and substantial utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor

activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to encoding polynucleotides and their uses for a protein that, as yet, has undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the KILCH polynucleotides or uses thereof in the instant application were, as of the filing date, useful for diagnosis, prevention and treatment of cancer, neurological disease, or reproductive disorders, as stated in the specification. Until some actual and specific significance can be attributed to the protein identified in the specification as KILCH, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

(11) Response to Argument

Appellants' arguments filed 9/17/03 have been fully considered but they are not persuasive for reasons of record and the following. Appellant argues that there is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis and that the Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function (Brief, page 4). This is a mischaracterization of the Examiner's position. Without having some basic knowledge or nexus, in contrast to precise or detailed knowledge, between the instant polynucleotides and some specific disease state, and whether an increase or decrease in expression is a desirable or undesirable outcome, and how a physician would specifically and substantially use that information for either diagnostic, prognostic, or therapeutic purposes, the usefulness of the gene expression analysis is in dispute. In other words, to ask a "real world" utility question, what action would my physician prescribe for me to take if upon gene expression analysis, my KILCH polynucleotides increased by 40% when I stopped taking testosterone (a hormone that can be used as a drug) to treat male infertility (a reproductive disorder)? The teachings of the specification cannot answer this, or any other medical question concerning any known disease state, regardless of whether that question concerns prophylaxis, treatment, or diagnosis of even a single specific disease. The Appellant cannot point to a single teaching in the specification where a specific increase or decrease in KILCH polynucleotides would lead the artisan to a single specific conclusion as to what the biological significance of

that finding would mean in a single specific disease state, and thus the invention lacks specific and substantial utility as being an invention only useful for further research.

Appellant's mere assertion that the disclosed encoded polypeptide KILCH has biological activities similar to known kinesin family members (whatever those biological activities may turn out to be) is not persuasive in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen in vivo, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end of the article). Similarly, PTH and PTHrP are two structurally

closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) discloses several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by only a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function; "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins" (see third sentence of abstract for the quotation, also see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multifunctionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. "Overpredictions are common because the highest-scoring database protein does not necessarily share the same or even similar functions" (Doerks et al., page

248). Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein, even if that small domain is in a non-functional region of the known protein (for example, assigning a new protein as being a functional enzyme based on matches to a known enzyme outside of the catalytic active site of the enzyme, even though the new protein lacks the known catalytic domain! This would be like assuming football fans in a stadium function at the athletic level of professional football players because their jerseys "match" the jerseys of the players on the field). Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted specific and substantial utility of KILCH as having kinesin family of protein or KLC biological activity because it is not known what the function of

KLC is in regards to kinesin as a whole and because the encoded KILCH polypeptides have never been actually produced and tested for any actual biological function. The only basis the disclosure has for asserting that the instant invention encodes for a protein that potentially possesses KLC functionality (whatever that might be) is based on a weak sequence similarity (only 66% between KILCH and human KLC). All of the aforementioned scientific documents discussed here cast serious doubt on Appellant's approach to ascribe to an unknown protein or the polynucleotides that encode it a specific functionality to this protein that has never been actually produced or expressed from its encoding nucleotides. In fact, as some of the prior art discussed here shows, an encoded protein's functionality may be the exact opposite of what was predicted from its sequence similarities to known proteins and that such determinations of biological significance or functionality can only be seen when the encoded protein is actually made, which was not done in the instant disclosure.

Appellant argues that the references used by the Examiner support the Appellant's position that homology or sequence identity is sufficient to establish a function and utility for the instant polynucleotides. Appellant's arguments are not persuasive because, as the Examiner has already indicated, Appellant has not taught what the function or utility of KLC is should the instant invention KILCH actually be a member of this kinesin family of proteins. Appellant appears to be engaging in a circular argument by stating that the instant invention, polynucleotides encoding KILCH, are useful and have utility because KILCH is a homolog of the known protein KLC, and KLC has "undisputed utility" (Brief, page 13). This is not correct; KLC does not have

"undisputed utility" (Brief, page 13) as Appellant asserts. The Examiner has disputed the utility of KLC beginning with the non-final Office Action filed 7/3/01 because the function of KLC itself is not known, and the utility of KLC has never been established, as Appellant readily concedes in the specification (page 3, lines 11-18). The same arguments that are made to demonstrate a lack of utility for the instant invention KILCH could be made for the prior art protein human KLC. KLC and its encoding nucleotides are not recognized in the art as having any utility for the diagnosis, prognosis, or treatment of any single specific cell proliferative, reproductive, or neurological disorder that is currently known, and contrary to Appellant's repeated assertions, there is no evidence of record from either the specification, the prior art of record, or Appellant's multiple responses to the Office Actions during the entire prosecution history of the instant Application to indicate that any such evidence exists associating human KLC or the instant KILCH to any known disorder or disease. This is as true in 2004 as it was at the time the Application was filed (March 7, 1998).

The Examiner would like to comment upon Appellant's arguments made in the Brief drawn to specific references, where possible. Concerning the allegation made by Appellant that "it is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small" (Brief, page 13), the Examiner cannot comment upon this reference specifically because Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) is not of record in the instant Application (a different Brenner et al. reference is of record, but it does not make such a claim). The absence of this reference notwithstanding, it must be pointed out that

the Examiner never asserted KILCH is unrelated to KLC or kinesin. In general, they are clearly structurally related. However, the rejection and this Answer set forth that the functional utility of KILCH cannot be established by asserting that it has the same functional utility as KLC because the functional utility of KLC is unknown. Even if the functional utility of KLC were known, and it is not, the fact remains that among related polypeptides in protein families, structural similarity is not predictive of functional similarity, so Appellant's arguments drawn to establishing the utility of KILCH by asserting it is the same utility as other kinesin family members such as KLC are fatally flawed for the multiple grounds set forth here.

Concerning the Tischer et al. and Benjamin et al. references concerning the divergent and sometimes opposite biological actions of VEGF and PDGF, the Examiner was providing evidence that members of the same protein family do not need to have the same biological function although both VEGF and PDGF share critical conserved cysteine residues, which are important in order that both VEGF and PDGF assume their biologically active conformations due to disulfide bonding between these conserved cysteine residues. If Appellant considers these share structural features unimportant for determining the biological activity of VEGF and PDGF, the unbiased observer must also cast doubt upon Appellant's assertion that KILCH must share similar biological activity with KLC (whatever that unknown activity may be) because of the shared structural features between KILCH and KLC, such as six conserved potential phosphorylation sites (see specification, page 16, lines 20-21).

Concerning the Massague and Vukicevic et al. references, Appellant's arguments are unpersuasive because Appellant argues that different members of the entire TGF superfamily of proteins are less closely related in sequence than KILCH and KLC. However, the Examiner would like to point out that the entire superfamily of TGF proteins was not what the Examiner was employing as evidence, but more specifically the proteins OP-1, TGFβ1, and BMP-2 (see page 10 of this Answer). OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions. OP-1 and BMP-2 are approximately 60% identical, just slightly less than the 66% identity between the instant KILCH and KLC that Appellant repeatedly contends is such a significantly high percentage identity that one of ordinary skill in the art would automatically impute the instant KILCH with the biological activity of KLC. Clearly, this is not the case here as the Examiner has supplied an example of scientific evidence to dispute Appellant's assertion.

Concerning the Pilbeam et al. reference, Appellant argues that only when non-homologous C-terminal regions are added that different biological activities emerge between the bone resorption proteins PTHrP and PTH. This argument is not persuasive because the same can be argued for the non-homologous regions between the instant invention KILCH and KLC because 34% of the amino acids between KILCH and KLC are non-homologous. According to Pilbeam, "because biological activity was thought to reside largely in the PTH homologous region, most studies have focused on PTHrP 1-34. However, recent studies have suggested that portions of the PTHrP peptide outside

the 1-34 region may have biological activities not shared with PTH (Mallette 1991) or biological activities opposing the actions of the PTHrP 1-34 fragment (Kaiser et al. 1992)" (Pilbeam, page 717, col. 2). The non-homologous regions between KILCH and KLC may very well determine the actual biological activity of KILCH, which is unknown at the present time.

Concerning the Kopchick et al. reference, Appellant's argument is not persuasive because Appellant argues that Kopchick is irrelevant because the observations in Kopchick resulted from a mutation which was deliberately engineered so as to alter an essential functional residue, and therefore Kopchick does not address the question of whether a naturally-occurring sequence (i.e. KILCH) retains the function of its homolog (i.e. KLC). Again, it is the Examiner's position that neither KILCH nor KLC have a specific or substantial known function that bestow upon them utility, and therefore Kopchick is relevant because Appellant cannot identify a single essential functional residue in the KILCH sequence, so if many residues differ between KILCH and KLC, it is quite possible that at least one of those amino acid substitutions between KILCH and KLC alter the biological function of the instant invention KILCH.

Concerning the Skolnick et al. reference, Appellant's argument is not persuasive because the Appellant is trying to use data derived from the active sites of enzymes to assign to KILCH the unknown biological function of KLC. Neither KILCH nor KLC are known to be enzymes or possess active sites, so the biological significance of the kinesin light chain repeat signatures in KILCH is unknown, much as the biological significance of the kinesis light chain repeat signature is unknown in KLC too.

Concerning the Bork and Doerks et al. references, Appellant's argument is not persuasive because the same errors that software robots make in assigning function to unknown proteins can be made by those same scientists who program the software robots with the rules they use themselves to assign biological functions to newly discovered proteins.

Finally, concerning the Smith et al., Brenner et al., and Bowie et al. references, none of Appellant's arguments are on point in refuting the Examiner's position that the Appellant has been engaged in circular reasoning, i.e. if KILCH is structurally related to KLC, then it must have the same utility as KLC has, except it is the Examiner's position that KLC itself does not have any patentable utility. Appellant is mistaken when, on page 23 of the Brief, Appellant states that "Bowie supports Appellants' assertions that significant sequence homology to a known kinesin light chain polypeptide coupled with the conservation of known active sites would lead one of skill in the art to conclude that KILCH is in fact a kinesin light chain polypeptide" because no known active sites are known for either KILCH or KLC because to know which "sites" are "active," one must know the biological activity the "site" is "active" for!

Appellant's arguments concerning toxicology testing are unpersuasive because the instant specification does not disclose toxicology testing as a utility for the instant KILCH polynucleotides. The only reference to toxicology testing in the specification is in relation to the testing of KILCH polypeptides and fragments thereof as therapeutic agents (see pages 37-38 of the specification). Obviously, KILCH polypeptides and fragments thereof are totally distinct and separately patentable inventions from the

nucleotides encoding KILCH polypeptides. Furthermore, microarrays for gene expression in regards to toxicology testing are not taught in the specification as filed. The portions of the specification dealing with microarrays are found on pages 42 and 51. These portions do not mention toxicology testing for drug development. Therefore, much of the Bedilion declaration, if not the vast majority, is arguing for utilities that are not taught in the specification as filed, and in fact, would constitute new matter. Notwithstanding the fact that the disclosure doe not teach toxicology testing as a utility for the instant invention, even if it did, as with drug testing, the significance of increases or decreases in KILCH polynucleotides in regards to toxicology cannot be ascertained because there are no teachings in the specification as to whether increases or decreases in KILCH polynucleotides are indicative of any particular drug or toxin, or whether an increase or decrease in expression of KILCH polynucleotides is a desirable or undesirable outcome in response to any toxin or drug so tested.

For example, if a compound is tested on a microarray comprising the claimed polynucleotides and affects expression of the polynucleotides negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would exacerbate the disease if administered. The test results also would not have meaning in terms of what specific disease is relevant. The asserted utility in gene expression monitoring assays is thus not substantial, because significant further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue.

Furthermore, since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides.

The specification does not support a specific and substantial utility regarding the claimed polynucleotides encoding KILCH and variants thereof for purposes unrelated to the asserted biological activity. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides or any known member of the KLC family. Nor does any of the prior art of record.

Appellant argues that any change in the instant polynucleotide level brought about by any potential drug candidate that is not targeted to KILCH gene function in a general screening assay is potentially indicative of toxicity and the drug candidate should be avoided. However, this asserted utility is true for any expressed polynucleotide that is not the target of the potential drug candidate and is not specific to the claimed invention.

Appellant fails to even acknowledge, yet alone respond to, the question posed by the Examiner on the top of page 11 of the final rejection filed 3/11/03 (repeated at the beginning of the "Response to Argument" section of this Examiner's Answer) about testosterone treatment in regards to the instant invention, further highlighting that the instant invention lacks any specific, substantial, well-established, or real world utility without further study and characterization.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ 696.

Appellant characterizes the Bedilion declaration as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, Appellant states that the Bedilion declaration describes how the claimed expressed polynucleotide can be used in gene expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Appellant quotes from the Bedilion declaration, that states that microarrays containing SEQ ID NO: 1-encoding and SEQ ID NO: 2 would be a more useful tool than microarrays lacking same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative, reproductive, and neurological disorders for such purposes as evaluating their efficacy and toxicity. This is not found to be persuasive. As an aside, it is noted that Dr. Bedilion is a consultant for Incyte Pharmaceuticals, Inc., the real party in interest in this appeal, and thus is a concerned party. Regarding the merit of the argument, any new polynucleotide can be used in a microarray, and thus this asserted

utility is not specific. Since the specification does not establish that either KILCH or KLC is expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues, this asserted utility is not substantial. In other words, the specification does not disclose that KILCH or KLC is expressed in tissues having cell proliferative, reproductive, or neurological disorders at altered levels or forms. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify disease states which correlate with altered levels or forms of the claimed polynucleotides. Therefore, this asserted utility is not substantial.

Appellant criticizes the examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. However, Appellant is mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the polynucleotide. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 as it has utility and is enabled as a colon cancer marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polynucleotides are

structurally related to KLC and hypothesizes that the claimed polynucleotides are involved in cell proliferative, reproductive, and neurological disorders, but the expression of the KILCH polynucleotide in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no disclosure that the claimed polynucleotides are expressed at altered levels or forms in any specific, diseased tissue. It is noted that the instant application was filed 07 March 1998. No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue. Also, no evidence has been brought forth that the claimed polynucleotides encode polypeptides having specific KLC activities.

Appellant argues that the use of KILCH polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Appellant states that there is no dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Appellant asserts that such is sufficient to establish utility for the claimed polynucleotide. This is not found to be persuasive. While the examiner agrees that any polynucleotide, including the claimed polynucleotides, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotides. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor. Such can be done with any orphan receptor, and thus the asserted utility is not specific. Furthermore, since the specification does not disclose a correlation between any disease or disorder and an

altered level or form of the claimed polynucleotides, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

Appellant refers to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that the application disclosing the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern analysis for measuring such. Specifically, Appellant quotes from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in gene expression monitoring to develop new drugs for the treatment of cell proliferative, reproductive, and neurological disorders. This is not found to be persuasive. The instant specification does not substantiate a link between the claimed polynucleotides and any specific cell proliferative, reproductive, or neurological disorder. The specification merely discloses that the claimed polynucleotides are structurally related to KLC, and that they are expected to be involved in cell proliferative, reproductive, and neurological processes (and thus, disorders). The specification does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polynucleotide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease

and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in diseased tissues; they are constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient.

Appellant refers to the opinion of Dr. Bedilion that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a more useful tool than a microarray lacking the claimed polynucleotide in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative, reproductive, and neurological disorders for such purposes as evaluating efficacy and toxicity. Again, this is not found to be persuasive, because the instant specification has not established that the claimed polynucleotides are expressed at altered levels or forms in diseased tissue as compared with the corresponding healthy tissue. If the claimed polynucleotide were in a microarray and a compound caused decreased expression of the claimed polynucleotide, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to exacerbate the disease? If it had been disclosed that the claimed polynucleotide is expressed at a higher level in a particular cell proliferative diseased tissue as compared with the corresponding healthy tissue, then the skilled artisan would know that a compound that decreased expression of the polynucleotide is a good potential cell proliferative disease drug. However, that is not disclosed by the instant specification. The claimed polynucleotides may very well be expressed at equivalent levels in healthy tissues. If that is the case, then the compound

being tested would not be a good potential drug. The claimed polynucleotides may also very well be expressed at a lower level in a particular cell proliferative diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased expression of the claimed polynucleotides would not be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Appellant discusses the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Appellant points to Dr. Bedilion's pages of text and numerous subparts explaining the importance of this technology. Appellant points to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing. This is not found to be persuasive. There is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims are directed to polynucleotides which have not

been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial.

Appellant urges that the Bedilion declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotide, because a microarray comprising the claimed polynucleotide would provide more useful results in the kind of gene expression monitoring studies that microarrays lacking the claimed polynucleotide. This is not found to be persuasive. The specification has not linked the claimed polynucleotide with any specific disease state or disorder, as discussed above and in previous Office Actions. Adding the claimed polynucleotide to a microarray would not make the microarray any more valuable than adding any other "orphan" polynucleotide. The asserted utility is not specific to the claimed polynucleotide.

Appellant argues that the examiner does not address the fact that, as described in the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Appellant concludes that the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. This is not found to be

persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for any polynucleotide. Thus, this asserted utility is not specific.

Appellant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Appellant reviews case law pertinent to the patentable utility of research tools. This is not found to be persuasive. Appellant's analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

Appellant argues that there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the effects of a potential drug for treating cell proliferative , reproductive, and neurological disorders. Appellant urges that, since the specification discloses the claimed polynucleotide to be expressed in cancer and immortalized cell lines, and the fact that the claimed polynucleotide is structurally related to KLC which is a part of

kinesin, the skilled artisan would have derived more information about a potential cell proliferative, reproductive, and neurological disorder drug candidate or potential toxin with the claimed invention than without it. Again, this is not found to be persuasive, because the specification does not disclose that the claimed polynucleotide is expressed at an altered level or form in any particular disease or disorder as compared to the corresponding healthy tissues. It may be useful to consider how broad the terms "cell proliferative, reproductive, and neurological disorders" are. Cell proliferative disorders include cancers, psoriasis, warts and slow-closing wounds. Reproductive disorders include male and female infertility, male erectile dysfunction, and frequent miscarriages. Neurological disorders include spinal cord injuries, Alzheimer's disease, blindness, deafness, and childhood mental retardation. Other than belonging to a broad genus of a "cell proliferative, reproductive, and neurological disorders," the recited diseases in each category have nothing in common other than belonging to a broad general category. Even if it could be assumed that the claimed polynucleotides play a role in cell proliferative, reproductive, or neurological disorders, determining which disorders are involved and how the claimed polynucleotides are altered during the disorder requires significant further research.

Appellant refers to Dr. Bedilion's discussion of the Brown et al. Patent (U.S. 5807522), attached to the declaration. Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. This is not found to be

persuasive. The Brown patent claims methods of forming microarrays. Microarray methods have patentable utility as a research tool, just like a scale or a gas chromatograph. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale, or the compound being analyzed by the gas chromatograph. Such is the situation at issue.

Appellant refers to other publications that discuss microarrays and gene expression technology with respect to drug screening and toxicology. Again, this is not found to be persuasive, because the arguments and evidence merely show that microarray technology is important and useful to the scientific community. These publications do not show that the claimed invention has a patentable utility. The use of the claimed uncharacterized polynucleotides in such studies would have provided no more information than the use of any other orphan polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide. Due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder, the asserted utility is also not substantial, as discussed above.

Appellant argues that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Appellant argues that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must be specific and substantial.

In this case, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Appellant's individual polynucleotides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

With regard to drug discovery and development, Appellant mentions expression profiling as one use of the claimed polynucleotide. Appellant refers to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Appellant is incorrect in asserting that the efficacy (ability of producing a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological significance of the polynucleotide(s) which is(are) being evaluated. Without this information, the results of the transcript image are useless because one would not know if the polynucleotide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either

present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Appellant argues that the utility of the claimed polynucleotide can be imputed based on the relationship between KILCH and KLC. Appellant urges that the examiner must accept that the homology demonstrates utility unless evidence or sound scientific reasoning is brought forth that a person of ordinary skill in the art would doubt utility. The argument is not found to be persuasive because evidence that a person of ordinary skill in the art would consider to doubt utility in this case has been brought forth. To clarify, the examiner never asserted KILCH is unrelated to KLC or kinesin. They are clearly structurally related. However, the rejection and this Answer sets forth that, among related polypeptides in protein families, structural similarity is not predictive of functional similarity. For example, Vukicevic et al. (1996, PNAS USA 93:9021-9026)

was cited in this response to Appellant's arguments as disclosing that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions. OP-1 and BMP-2 are approximately 60% identical. It is noted that OP-1, BMP-2 and GDF-9 are all TGF-β family members. Kopchick et al. (U.S. Patent 5,350,836) was cited as disclosing several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid. These pairs of polypeptides are 99.5% identical. Therefore, whereas it is credible that KILCH is related to KLC, the relationship is structural. Functional relatedness is not supported in the face of evidence in the art that structurally related polypeptides in protein families are frequently dissimilar functionally.

Appellant argues that a showing of commercial success or actual use establishes utility. As argued previously, many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors.

Appellant asserts that the examiner improperly refused to impute the utility of kinesin homolog family to the claimed invention. Appellant urges that the case law requires only that the class not contain a substantial number of useless members. Appellant urges that the examiner has treated KILCH as if it were in the general class of all polynucleotides, rather than the kinesin homolog class. Appellant concludes that the examiner has not presented any evidence that the kinesin homolog class of proteins

has any, let alone a substantial number, of useless members. This is not found to be persuasive. The kinesin family is functionally highly diverse, as evidenced by the references made of record in the rejection to the differences between KHC and KLC. When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here.

Appellant urges that knowledge that KILCH is a KLC homolog is more than sufficient to make it useful for the diagnosis and treatment of cell proliferative, reproductive, and neurological disorders. Appellant states that KLC has been shown to be expressed in cancer cells. Appellant concludes that these facts must be accepted as true in the absence of evidence or sound scientific reasoning to the contrary. This is also not found to be persuasive. Mere expression in a cancer cell does not mean that the polynucleotide is an appropriate target for drug development or toxicology testing. Cancer cells express many polynucleotides, such as constitutively expressed polynucleotides, which are not appropriate targets. The specification has not disclosed a specific disease or disorder of any type wherein the claimed polynucleotides are expressed at altered amounts or forms relative to the required control healthy tissue. Significant further research would be required of the skilled artisan to identify such a disease or disorder. Therefore the asserted utility is not substantial.

Therefore, for reasons set forth above, Appellant's arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

SG

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March 8, 2004

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